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Autism in patients with propionic acidemia

Peter Witters [a], Eric Debbold [b], Kea Crivelly [b], Kristel Vande Kerckhove [a], Karen Corthouts [a], Brett Debbold [b], Hans Andersson [b], Lena Vannieuwenborg [c], Sam Geuens [c], Matthias Baumgartner [d], Tamas Kozicz [b,e], Lisa Settles [f], Eva Morava [a,b,*]

[a] Department of Pediatrics, Metabolic Center, University Hospitals Leuven, Leuven, Belgium
[b] Hayward Genetics Center, Tulane University School of Medicine, New Orleans, LA, USA
[c] Department of Psychology, Metabolic Center, University Hospitals Leuven, Leuven, Belgium
[d] Division of Metabolism, Children's Research Center, University Children's Hospital Zurich, Zurich, Switzerland
[e] Donders Institute for Brain, Neuroscience, Radboudumc, Nijmegen, The Netherlands
[f] Department of Psychiatry, Tulane University School of Medicine, New Orleans, LA, USA

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ABSTRACT

Certain inborn errors of metabolism have been suggested to increase the risk of autistic behavior. In an animal model, propionic acid ingestion triggered abnormal behavior resembling autism. So far only a few cases were reported with propionic acidemia and autistic features. From a series of twelve consecutively diagnosed cases with propionic acidemia, we report on eight patients with autistic features.

The patients were followed 2–4 times a year and underwent regular clinical, dietary and laboratory investigations. Psychological evaluation was performed every second to fourth year.

All patients were compliant with the standard diet and carnitine supplementation. None of the patients had frequent metabolic decompensations. From the metabolic factors known to impact neuropsychological outcome we detected chronically decreased valine levels and altered valine to leucine ratios in five out of the eight patients. Recurrent lactic acid elevations were present in six out of the eight patients. Five of the eight patients were diagnosed with Autism Spectrum Disorder, four of them had pathogenic variants in *PCCB*. Disorder according to DSM-IV and/or DSM-5 criteria. One of the patients diagnosed with propionic acidemia by newborn screening had the most significant behavioral features and another was diagnosed with Autism Spectrum Disorder prior to propionic acidemia.

We hypothesize that chronic suboptimal intracellular metabolic balance may be responsible for the increased risk for autistic features in propionic acidemia. We propose that patients diagnosed with propionic acidemia should be screened for Autism Spectrum Disorder.

1. Introduction

Propionic acidemia (PA) is a severe organic acidemia, characterized by acute episodes of metabolic acidosis, ketosis, lactic acidemia, hyperammonemia, lethargy, basal ganglia involvement, and seizures. Even well treated patients might develop growth delay, developmental and speech delay. Long term outcome is often characterized by intellectual disability [1,2]. Recurrent episodes of pancreatitis, muscle weakness and metabolic cardiomyopathy occur in a high percentage of cases, especially in those with insufficient therapeutic compliance [3]. Even the most adequately treated patients might develop neurologic symptoms including psychomotor retardation, speech delay, dystonia and even ischemic strokes of the basal ganglia [2]. Behavioral changes are relatively common in adolescent patients with PA, though Autism Spectrum Disorder (ASD) has been only reported in a single patient.

ASD is a complex neurodevelopmental disorder, characterized by social impairments, communication difficulties, and restricted, repetitive, and stereotyped patterns of behavior. Several inborn errors of metabolism have been described as increasing a patient's risk for ASD, including lysosomal storage diseases, disorders of the creatine synthesis, disorders of purine and pyrimidine metabolism or dysfunction of the urea cycle, but autistic features are not frequently reported in organic acidemias [5,8,9,10,11]. With the growing frequency of patients being diagnosed with ASD, sometimes it is difficult exclude a coincidental diagnosis of autism in certain metabolic conditions from comorbidity, especially in case of intellectual disability. The incidence of metabolic disorders in autistic patients is not known, but is estimated as high as

* Corresponding author at: Hayward Genetics Center, Tulane University School of Medicine, New Orleans, LA, USA; Department of Pediatrics, Metabolic Center, University Hospitals Leuven, Leuven, Belgium.
E-mail address: emoravakozicz@tulane.edu (E. Morava).

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5%, while in the general population cumulative occurrence of inborn errors of metabolism is closer to 1 in 800[5]. In recent guidelines for the treatment of propionic acidemia, evaluation and monitoring for autism is not yet included [2].

Interestingly, studies evaluating the effects of elevated propionic acid in rats have suggested a possible connection with autism [6,7]. Propionic acid administered systemically or by intracebro-ventricular injection to adult rats produced a rapid induction of repetitive movements, hyperactive activity, and seizure activity along with neuro-pathological and biochemical similarities to human ASD [6]. The mechanisms by which elevated levels of propionic acid affect the CNS are unknown, but possible candidates include interference with cellular metabolism, increased inflammatory cytokines and the reduction of intercellular gap-junctional communication.

Here we report on eight patients with autistic features and propionic acidemia from a case series of twelve consecutively diagnosed propionic acidemia patients. Biochemical and clinical information was collected and evaluated whether a risk factor for autism could be found.

2. Methods

2.1. Patient selection

A total of eight patients with propionic acidemia (PA) were evaluated in detail in this study. The inclusion criteria were the biochemical diagnosis of propionic acidemia confirmed in fibroblasts, in two centers, between 1995 and 2015. Twelve patients were diagnosed during the twenty years period. Four patients were excluded from the data analysis due to the unavailability of sufficient detailed clinical/metabolic and behavioral data. The patients' age range was between 3 and 20 years, with a median age of 7.5 years. Patients 6 and 7 are fraternal twins, patients 4 and 9 and Patient 10 and 11 were brothers. Seven patients were male, and one was female (Table 1). With regards to therapy, all of the patients followed a strict protein-restricted diet, with a maximum daily intake of 0.8–1 g/kg/day of natural protein and high caloric intake (110–138 cal/kg/day). All patients received carnitine (50–100 mg/kg/day) and biotin (10 mg/day) supplements. All but one patient received amino acid based metabolic formula, free of the precursor amino acids (Met, Val, ILe, Thr) additional to protein-free metabolic formula with extra sources of calories through carbohydrates and fats.

2.2. Prognostic factors

Prognostic factors known to play a role in PA patients' long-term outcome were retrospectively evaluated in our cohort. We included clinical, neurologic, and neuropsychiatric features, disease history and disease severity, anomalies on brain imaging, developmental features, behavioral problems, the presence of autistic features or the diagnosis of Autism Spectrum Disorder, and metabolic laboratory values in

Table 1
Clinical and genetic information in eight patients with features of the autistic spectrum, out of a twelve patients' cohort diagnosed with propionic acidemia (four patients; Patient 9–12 were not included in the analysis due to insufficient detail on neurodevelopmental and biochemical data).

Patient	Sex	Age (years)	Diagnosis	[e]Metabolic crises/year	Motor delay	Intellectual disability	Speech development	CNS involvement	Basal ganglia involvement	Organ involvement	[g]Pathogenic variants (cDNA and protein)
1.	M	3[c]	NBS	2	Mild	N/A	Absent	Hypotonia[f]	Infantile	None	*PCCB* c.1209 + 3A> G/p.V356E403del c.1209 + 3A> G/p.V356E403del
2.	M	4	NBS	2–3	Severe	Moderate	Absent	Hypotonia[f]	Neonatal	None	*PCCB* c.562G>A/p.G188AR c.562G>A/p.G188R
3.[b]	M	4	NBS	0	Moderate[h]	Moderate	Absent	None	None	None	*PCCB* c.638C>T/p.P228L c.638C>T/p.P228L
4.[a]	M	7	3 years	0	None	None	Delayed	None	None	None	*PCCB* c.683delC/p.P228L c.683delC/p.P228L
5.	M	8	7 days	2–3	Moderate	Moderate	Delayed	None[d]	None	None	*PCCA* c.1891C>G/p.G631R c.1891C>G/p.G631R
6.[a]	M	11	2.5 months	1–2	Mild	Moderate	Delayed	Abnormal gait[d]	None	None	*PCCB* c.1218_1231del14ins12 p.G407Rfs*14 and [h]c.479A>G p.D160G
7.[a]	M	11	NBS	2–3	Mild	Mild	Delayed	Abnormal gait	None	Arrhythmia	*PCCB* c.1218_1231del14ins12 p.G407Rfs*14 and [h]c.479A>G p.D160G
8.[a]	F	21	3 months	1	Moderate	Moderate	Delayed	Spasticity[d]	None	Pancreatitis	N/A
Patients with insufficient data for analysis											
9.	M	9	5 years	0	None	None	Normal	None	None	None	*PCCB* c.683delC/p.P228L c.683delC/p.P228L
10.	M	7	5 days	1–2	None	None	Delayed	None	None	None	*PCCB* c.1210G>A p.E404K c.1210G>A p.E404K
11.	M	3[c]	3 years	NA	None	None	Normal	None	None	Pancreatitis	*PCCB* c.1210G>A p.E404K c.1210G>A p.E404K
12.	F	4[c]	10 days	2–4	Severe	N/A	Absent	Hypotonia	None	Pancreatitis	*PCCA* c.923dupT/p.L308fs c.923dupT/p.L308fs

NBS denotes newborn screening test positive for Propionic academia.
Patients 6 and 7 are fraternal twins, patients 4 and 9 and Patient 10 and 11 were brothers.
[a] Diagnosis of autism (ASD) according to DSM-IV (Lord et al., Autism Diagnostic Observation Schedule (ADOS-2), 2nd Ed. 2000).
[b] Diagnosis of autism (ASD) according to DSM-5 criteria (Sparrow, Cicchetti, Balla, Vineland Adaptive Behavior Scales-2nd Ed. 2005).
[c] Patient deceased.
[d] Propionic acidemia related early coma episode.
[e] Number of metabolic disarrangements in the first 4 years of life.
[f] Central hypotonia.
[g] Previously described mutations in all but one patient (Kraus et al., J Inherit Metab Dis (2012) 35:51–63; Perez et al., Mol Genet Metab 2003,78: 59; Lamhownwah et al., Genomics. 1990, 8:249).
[h] So far unreported, predicted pathogenic variant.

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blood and urine as they were collected throughout each patient's treatment two to four times a year depending on their age.

2.3. Metabolic and genetic factors

We studied the different clinical and biochemical parameters used to monitor the course of propionic acidemia in eight patients from a case series of twelve consecutively diagnosed propionic acidemia patients, treated from 1995 till present. Biochemical parameters included blood levels of lactate, amino acids (with focus on alanine, isoleucine, leucine, valine, and methionine), ammonia, plasma C3 acyl-carnitine and methylcitrate and OH-propionate in the urine. Clinical data included the age and type of diagnosis, disease history, treatment history, multisystem involvement and MRI changes. Except for in one patient DNA sequence analysis was requested.

2.4. Neuro-psychological evaluation

Developmental assessment is systematically implemented in the multidisciplinary follow-up of metabolic patients and contains a multidisciplinary assessment at the age of 1 year; 2,5 years; 6 years and 12 years. Age-adapted instruments are used such as: Bayley Scales for infant development II (BSID-II), Wechler Preschool and Primary Scale of Intelligence III NL (WPPSI II-NL) and Wechsler Intelligence Scale for Children III-NL (WISC III-NL) for assessment of mental development and the Reynell Developmental Language Scales and Dutch Non-Speech Test for assessment of language development. The Peabody Developmental Motor Scales second edition was used to assess motor capacities. Because some of the patients were unable to cooperate with age-appropriate intelligence measures at the 4 year visit, the Bayley Scales of Infant and Toddler Development-3rd Edition (BSID-3; Bayley, 2006) was administered to calculate age equivalents only. Categorization of intellectual disability was done according to the ICD-10 categorization system (Table 2, Supplementary Tables 1 and 2).

When the possibility of ASD was assumed based on clinical observations in our European patients, a referral was made to a specialized diagnostic center for further neuropsychiatric studies. Diagnostic methods contained a semi-structured interview with parents, play observation, class observation, evaluation by a speech therapist, and questionnaires for parents and teachers. In the American patients ASD was evaluated by data gleaned through a detailed developmental interview, administration of the appropriate module of the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) and the Vineland adaptive behavior measure (Tables 1 and 2).

3. Results

3.1. Clinical course and prognosis

Of the twelve patients we studied, eight had sufficient information for this retrospective study. These were also the patients who showed autistic features. Of these eight patients five were diagnosed in the neonatal period. Four presented with positive newborn screens and minimal symptoms. One had clinical symptoms before newborn screening results. The remaining 3 patients presented between 2.5 months and three years with symptoms of a metabolic coma and were clinically diagnosed (Table 1). Five of the patients continued to have recurrent metabolic decompensations requiring hospital admissions yearly. All patients were compliant with treatment, followed the prescribed diet and took dietary supplements. One of the patients had up to 3 exacerbations yearly. Interestingly, one of the patients later diagnosed with ASD had no metabolic crises or episode of coma during the clinical course. One patient had a transient cardiac involvement (a rhythm abnormality with long QT syndrome) and one patient had episodes of pancreatitis. None of the patients with ASD had systemic organ involvement at the time of analysis.

3.2. Metabolic parameters

Metabolic parameters were evaluated to look for possible abnormalities, which could be associated with autistic features in PA. We used 85 pooled data points from individual blood sampling moments and urine collection data.

Recurrent lactic acidemia was present in 35% of the measured lactate levels (30/85) in the patients. No chronic lactic acidemia was noted in any of the children. Elevated blood alanine levels were sporadic, in 9.4% of the data points. Blood isoleucine levels were almost all normal, with 8% low normal, but within the normal range. Leucine levels were also almost always normal, with less the 5% low normal. Interestingly 70% of the biochemical values (60/85) showed decreased valine levels, (mean 62, range 10–150) (control 100–480 mmol/l) (Supplementary Fig. 1). The mean valine/leucine ratio using all pooled data points was 1.3 (ranged between 0.9 and 1.5, control range 1.5–2). Only 5% of the patient's data showed a low methionine level. From the pooled patient data 40% (34/85) showed an elevated ammonia level, with the highest level at 200 μmol/l (control range < 35 μmol/l) but none had a chronic elevation. None of the patients had chronically elevated glutamine levels.

None of the patients had C3 carnitine levels above 10 μmol/l (control <3.3 μmol/l) or methylcitrate levels above 200 mmol/mmol

Table 2
Intellectual disability assessment in eight patients with autistic features.

Patient nr	Sex	Eval. age	Instruments	Outcome	Developmental age	Intellectual disability	
Patient 1	M	20 months	Peabody scale	Developmental index <75	16 months	N/A	Autistic
Patient 2	M	20 months	BSID-II NL	Developmental index <55	5.5 months	Moderate	Autistic
		25 months	BSID-II NL	Developmental index <55	6 months	Moderate	
		30 months	BSID-II NL	Developmental index <55	6.5 months	Moderate	
Patient 3	M	26 months	Adaptive Behavior Scale	Developmental index <70	18 months	Mild	ASD
		56 months	BSID-3	Developmental index <60	34 months	Moderate	
		56 months		Developmental index <55	22 months	Moderate	
Patient 4	M	4 years	School admission	Attends regular school	Age appropriate	None	ASD
Patient 5	M	4 years	Wechsler	60B	2.5 years	Moderate	Autistic
Patient 6	M	66 months	SON-R	SON-IQ = 50	36 months	Moderate	ASD
Patient 7	M	66 months	Tandem	/	21 months	Mild	ASD
Patient 8	F	6 years	Wechsler	52EL	3 years	Moderate	ASD

SON-R, Snijers-Oomen nonverbal intelligence test-Revised; BSID-II NL, Bayley Scales of Infant Development 2nd edition Dutch version.
Vineland Adaptive Behavior Scale 2nd Edition Sparrow et al., 2005.
Bayley Scales of Infant and Toddler Development-3rd Edition (BSID-3; Bayley, 2006).
Wechsler Intelligence Scale for Children: A average, LA low average, B borderline, EL extremely low.

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creatinine and 3-hydroxypropionate above 300 mmol/mmol creatinine after the initial diagnosis.

3.3. Mutation analysis

Results were available in 11 patients from the total cohort, and in 7 out of the 8 patients studied in detail. The following known pathogenic variants were detected: in the *PCCA* gene in Patient 1 a homozygous c.1209 + 3A>G; p.V356E403del and in Patient 5 homozygous c.1891C>G; p.G631R, without autistic features. In the *PCCB* gene the c.638C>T; p.P228L known pathogenic variant was found in Patient 3, Patient 4 and Patient 9 in homozygous form, and c.562G>A; p.G188R known pathogenic variant in Patient 2.

Patients 3 and 4 were diagnosed with autism. Patient 4 and 9 were brothers. Although in Patient 9 only insufficient data was available for metabolic analysis, he had a normal development, attended regular education and no autistic features.

Compound heterozygous known variants in *PCCB* were detected in the fraternal twins, both known with autism (c.1218_1231del14ins12; p.G407Rfs*14/c.479A>G; p.D160G). In summary all patients with autism had a pathogenic variant in *PCCB*. The available variants and mutation references are depicted in Table 1.

3.4. Neuro-psychological features

Neurologic involvement was quite variable in the cohort. Two of the patients had a fully normal motor development. Several patients had mild to moderate motor delay, and most patients had mild to moderate intellectual disability. Only one patient had normal intelligence. One of the five patients (Table 1) was diagnosed with ASD first, before the diagnosis of PA was established. Other neurologic features included absent speech in three, hypotonia in two, abnormal gait in two, and spasticity in the oldest, female patient. One patient had transient abnormalities at the age of 3 months by MRI imaging. The other patient, the youngest of the cohort, also showed basal ganglia involvement with abnormal signal intensity of the caudate nuclei on CT. The two patients with basal ganglia involvement were not the ones who had a formal diagnosis of ASD. None of the patients showed any clinical regression during the course of the disease.

Autistic features were present in all the patients including repetitive movements or hand flapping, ritualistic behavior, stereotypic behavior (three patients), abnormal social interaction (seven patients), communication difficulties (all patients), and inflexibility in planning (all patients). Four patients were diagnosed with an Autism Spectrum Disorder between the age of 2 and 5 years. One patient was diagnosed with ASD at 2.5 years before the diagnosis of PA. In summary autistic features were present in all eight patients, with five having the formal ASD diagnosis, four of which were diagnosed between 2 and 5 years, and one was diagnosed even before diagnosed with PA (Tables 1 and 2).

4. Discussion

While the etiologic factors in most patients with symptoms in the autistic disorder spectrum are not fully understood, changes in amino acid metabolism and organic acid concentrations have been reported in animal models mimicking autistic symptoms [6,7]. Furthermore, amino acid levels in autistic patients have been reported as significantly different from non-autistic control groups [3,5,14]. Inborn errors of metabolism such as propionic acidemia have been suggested to increase the risk for autism in a few cases [4,18]. Interestingly in another case report partial biotinidase deficiency, leading among others to decreased activity of propionyl-CoA carboxylase, the defective enzyme in PA, could also cause ASD [13]. We evaluated eight PA patients with autistic features and investigated their biochemical and metabolic control, diet, and their clinical history.

We hypothesized that patients with early diagnosis, treatment, and good clinical and metabolic management will be less likely to develop neurologic and neuropsychological features, including autistic features or ASD in propionic acidemia. Early diagnosis, however did not seem to have a fully preventive effect on a complicated behavioral outcome. One of the patients diagnosed with propionic acidemia by NBS and with ASD has never had metabolic crises, or coma episodes during the clinical course. None of the patients diagnosed with ASD had systemic organ involvement, or basal ganglia involvement, which are known to correlate with insufficient metabolic control. In general, however, patients with a later diagnosis and recurrent metabolic decompensations were more frequently diagnosed with developmental delay and also with ASD.

Propionic acidemia is a metabolic disorder that affects not only the branched chain amino acid and odd chain fatty acid degradation but also has a negative effect on the normal function of both the urea cycle and the citric acid cycle, and can lead to neurotransmitter imbalance, and abnormal energy metabolism [3]. In our patient cohort 30–40% of the pooled metabolic data showed elevated lactate and or ammonia levels, without chronic lactic acidemia or hyperammonemia. Lactic acid elevation is a common metabolic sign in many patients with ASD. Mitochondrial dysfunction, a known consequence of propionic acidemia, has also been associated with autism [12]. Hyperammonemia has been associated with autistic features in mild, or insufficiently treated urea cycle disorder patients. Although some of the metabolic results we describe were collected during metabolic decompensation periods and do not mirror the general metabolic balance, we propose that mitochondrial involvement could play a significant role in the development of autistic features.

Physiologic blood and CSF amino acid concentrations are essential for normal neurodevelopment. Several studies on amino acid levels in ASD patients demonstrated significant changes in amino acid concentrations, like low methionine or high alanine levels [14]. In our small cohort we could not confirm these amino acid concentration changes. However, we did find a very interesting alteration, low normal serum valine levels and a decreased valine to leucine ratio, detected in the majority of our patients. Similar results have been previously documented in PA [15] and MMA and may be a consequence of supplementation with leucine enriched, precursor free amino acid mixture (Manoli et al., Genetics in Med 2016). Additionally, the primary enzymatic defect affects intra-mitochondrial physiology which, in the neuron, is impossible to monitor with standard metabolic methods.

A normal valine to leucine ratio is important for branch-chained amino acid (BCAA) transport through the blood brain barrier and for normal neurotransmitter concentrations. Abnormal BCAA transport has been suggested to lead to abnormal psychological development in other disorders such as Maple Syrup Urine Disease [8]. Some of the observed changes in BCAA ratios might be a consequence of the use of amino acid based metabolic formulas that are free of the amino acids, valine, methionine, isoleucine and threonine in PA patients.

No genotype phenotype analysis was possible in our small cohort. However, interestingly all patients diagnosed with autism and an available mutation result had a pathogenic variant in *PCCB*. There was one particular mutation, found in homozygous state in two unrelated patients with the diagnosis of autism. Both patients had a mild metabolic phenotype, and no recurrent metabolic crises. However the same mutation was found in the brother of one of these patients, without developmental delay, metabolic crises and without any autistic features.

There are several different inborn errors of metabolism, where the associated ASD has been hypothesized to correlate with a neurodevelopmental defects and congenital brain anomalies, like congenital disorders of glycosylation (CDG) or Smith Lemli Opitz syndrome [9,10]. However, no similar brain abnormalities have been observed in our patients with PA. Basal ganglia involvement is also associated with higher frequency of autistic features, but we didn't find correlation between basal ganglia abnormalities and ASD in our small cohort [16].

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Four of our five patients diagnosed with ASD had a mild or moderate motor delay and intellectual disability (Table 1). One should also emphasize that in the general population intellectual disability has 75% comorbidity with autism [17]. However in our cohort, patients without intellectual disability also showed autistic features or ASD. The current data presented would indicate an ASD prevalence higher than the 1 in 68 in the general population (CDC, 2016), suggesting a higher incidence of ASD in the PA population. The American Academy of Pediatrics suggests routine screening of children at 18 and 24 months or when a caregiver and/or physician raises a concern. PA has neurodevelopmental implications that can be similar to the symptoms observed in ASD (i.e., intellectual disability, language delays), which makes screening an important element in the care of an individual with PA.

Previous studies on amino acid analysis in ASD demonstrated diverse changes in levels of different amino acids, which could represent comorbidities, like nutritional deficiencies, or signs of mitochondrial dysfunction, but could also represent metabolic phenotypes, and biomarkers for ASD [14]. This has been also suggested in several publications evaluating the possible correlation between gastrointestinal propionic acid production and autism [18]. Abnormal branch chained amino acid ratios have also been correlated with poor neuropsychologic outcome [8]. With the increasing reported frequency of ASD in the pediatric population one cannot rule out a possible coincidence of the diagnosis of ASD in patients with propionic acidemia [19]. Given a population autism rate of approximately 0.005, the chance of this occurring with no connection with PA is 4.34×10^{-13}. In our case series five out of eight propionic acidemia patients exhibited autism, strengthening the possible correlation between propionic acidemia and ASD.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ymgme.2016.10.009.

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